SYNTHESIS OF ANNULATED FURANS WITH VARIOUS 3-SUBSTITUENTS VIA A SEQUENTIAL FURANNULATION/ENE ROUTE

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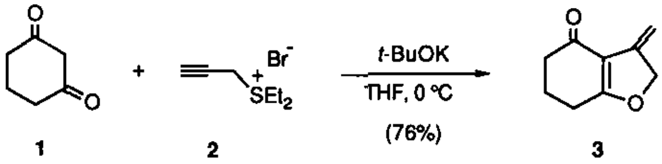
Abstract—Annulated furans with various 3-substituents were synthesized through the one-step synthesis of **3** and its ene reactions with enophiles.

Polysubstituted furans occur frequently in terpenoids and serve as the versatile building blocks in organic syntheses. In recent years, numerous successful methods have been developed to synthesize polysubstituted furans,[1] however, in general, direct introduction of the substituent at C-3 or C-4 position of furan is difficult. This is because lithiation and attack of electrophile occur predominantly at C-2 or C-5 position. Several procedures have been devised in order to overcome this difficulty,[2] whereas 3,4-disubstituted furans have mainly been prepared by the annulation of acyclic precursors which have substituents at those positions destined to become the C-3 and C-4 positions.[1] Recently, we reported a convenient single-step convergent approach to the annulated furan ring system by the reaction of an enolate anion of cyclic 1,3-diketone and allenic sulfonium salt.[3] As an application of our furan ring construction method, we now describe an efficient synthesis of annulated furans with various substituents at C-3 position *via* a sequential furannulation / ene route. This synthetic procedure would be comparable to the direct introduction of the substituent at C-3 position of furan.

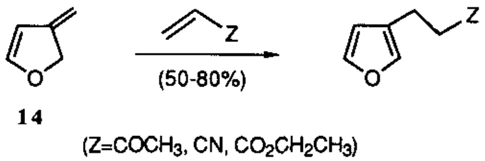
Compound (3) served as an "ene" was readily prepared by the reaction of 1,3-cyclohexanedione (1) and diethyl prop-2-ynyl sulfonium salt (2) with *tert*-BuOK in 76 % yield (Scheme I).[4] Compound (3) was extremely acid-sensitive and somewhat heat-sensitive, and easily isomerized to bicyclic 3-methylfuran, however **3** could be stored in a refrigerator (-20 °C) for several months without isomerization.

Ene reaction of **3** with various enophiles proceeded under relatively mild conditions and are summarized in Table I. Highly reactive enophiles such as diethyl azodicarboxylate (entry 1), tetracyanoethylene (entry 2), Eschenmoser's salt (entry 3) and ethyl glyoxylate[5] (entry 4) reacted with **3** even at room temperature to give the corresponding ene adducts (**4**-**7**) within 1 hour in high yields. In the reactions of Eschenmoser's salt (entry 3)



Scheme I

and ethyl glyoxylate (entry 4), the trace acid contaminated in the enophiles caused the isomerization of **3**, however it could be suppressed by the addition of sodium acetate in the reaction system as an acid scavenger. Sodium acetate was also effective in other ene reactions (entries 7, 8 and 9). Reaction of **3** with methyl vinyl ketone (entry 5), acrolein (entry 6) and dimethyl fumarate (entry 7) proceeded under the condition of heating in toluene (110 °C). In the reaction of acrolein, the olefin-ene reaction was occurred predominantly to give **9** in 83 % yield and the adduct of carbonyl-ene reaction (**10**) was obtained in only 2 % yield. Reaction of **3** with acrylonitrile and propionaldehyde proceeded under somewhat severe conditions (heating in xylene at 150 °C) and afforded ene adducts (**12**) and (**13**) in 87 % and 52 % yields, respectively. Ene reaction with ethyl acrylate, a low reactive enophile, did not proceed even at 180 °C after 20 h. All the ene adducts were identified by the spectral analyses (^{1}H nmr, ir, mass).



Scheme II

Recently, Miles *et al.* reported the ene reaction of **14** (as a 4 : 1 mixture with 3-methylfuran) with a few enophiles (Z=$COCH_3$, CN, $CO_2CH_2CH_3$)[6, 7] and obtained ene adducts in 50-80 % yield under the condition of refluxing in CH_2Cl_2 (Scheme II). These results are contrast to our findings described above, since the ene reaction of **3** needed more severe conditions. This is probably due to the stability of **3** which reduces the driving force for rapid ene reaction leading into the more stable aromatic furan system.

In conclusion, the procedure reported herein provided a new access to a facile and practical synthesis of annulated furans with various 3-substituents. The synthetic application of these bicyclic furans is under investigation in our laboratory.

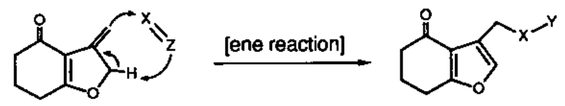
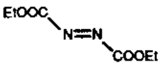
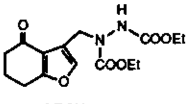
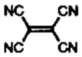
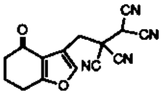
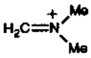
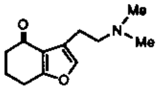
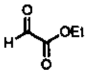
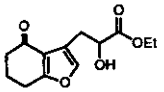
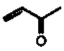
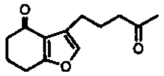
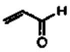
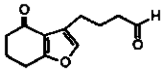
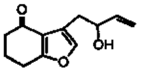
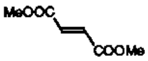
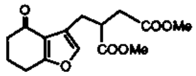
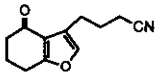
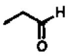
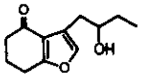


Table I. Ene Reaction of 3 with Various Enophiles

entry	enophile	time (hour)	temp. (°C)	furan (yield)
1		1	r.t.	 **4** (97%)
2		0.5	r.t.	 **5** (88%)
3a)		0.5	r.t.	 **6** (93%)
4a)		1	r.t.	 **7** (96%)
5b)		6	110	 **8** (86%)
6b)		3	110	 **9** (83%)  **10** (2%)
7a)		24	110	 **11** (88%)
8a),b)		12	150	 **12** (87%)
9a),b)		18	150	 **13** (52%)

a) Sodium acetate was added to trap the trace acid. b) Reaction was carried out in a sealed tube.

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4. Preparation of compound (**3**) is as follows: To a solution of *tert*-BuOK (4.8 g, 42.8 mmol) in anhydrous THF (100 ml) was added dropwise 1,3-cyclohexanedione (4.0 g, 35.7 mmol) dissolved in anhydrous THF (40 ml) over 10 min. After stirring for 30 min at room temperature, the mixture was cooled to 0 °C and diethyl prop-2-ynyl sulfonium bromide (11.2 g, 53.6 mmol), which was prepared from diethyl sulfide and propargyl bromide, was added. The reaction mixture was stirred for 6 h at 0 °C. After dilution with water (200 ml), the resulting mixture was extracted with Et_2O (150 ml x 3). The combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent in vacuo, the residue was purified by chromatography on Al_2O_3 (300 g) (hexane / ethyl acetate = 30 : 1 → 10 : 1) to give 4.68 g of **3** as a pale yellow solid. This material was recrystallized from hexane-AcOEt to give 4.06 g (76%) of pure **3** as colorless crystals: mp 71-71.5 °C; ^1H nmr ($CDCl_3$, 270 MHz) δ 5.66 (t, J=3.3 Hz, 1H), 5.07 (dd, J=3.3, 2.6 Hz, 2H), 4.83 (t, J=2.6 Hz, 1H), 2.55 (t, J=6.3 Hz, 2H), 2.42-2.38 (m, 2H), 2.11-2.02 (m, 2H); ir ($CHCl_3$) 1650, 1600, 1420, 1400 cm^{-1}; ms (EI) *m/z* 150 (M^+). Anal. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 71.79; H, 6.78.
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